PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference fp18189	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. PCT/AU2003/000972	International Filing Date *(day/month/year)* 31 July 2003	Priority Date *(day/month/year)* 1 August 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl. [7] C07D 233/90; A61K 31/4172; A61P 1/04, 3/06, 9/10, 9/14, 17/02, 25/28, 29/00, 39/00

Applicant

BIODIEM LIMITED et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of **5** sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of **3** sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [X] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of the report
5 February 2004	5 July 2004
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **D.A. LALLY** Telephone No. (02) 6283 2533

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/000972

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1 to 4, 6 to 10, 12 to 93,** as originally filed,
pages , filed with the demand,
pages **5 and 11** received on with the letter of **28 June 2004**

☒ the claims, pages **94, 95 and 97 to 100** as originally filed,
pages as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **96,** received on with the letter of **28 June 2004**

☒ the drawings, pages **1/6 to 6/6,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report

INTERNATIONAL PR[redacted]INARY EXAMINATION REPORT

International application No.
PCT/AU2003/000972

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1 to 50**	**YES**
	Claims	**nil**	**NO**
Inventive step (IS)	Claims	**1 to 50**	**YES**
	Claims	**nil**	**NO**
Industrial applicability (IA)	Claims	**1 to 50**	**YES**
	Claims	**nil**	**NO**

2. Citations and explanations (Rule 70.7)

Document 1: Buylon, V.V.. Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (1995), (1), 21-3. "Central mechanisms of neurogenic gastric lesion and its drug correction".
Document 2: Buloin, V.V, *et al.* Eksperimental'naya Terapiya I Klinicheskaya Farmakologiya(1994), 57(3), 18-20. "Effects of some neurotropic agents on lipid peroxidation in the heart and stomach in their neurogenic damages".
Document 3: Bulyusin, V.Y., *et al.* Byulleten Eksperimental'noi Biologii I Meditsiny (1988), 106(11), 568-70. "Therapy of experimental lesions of the duodenum with nootropic action".
Document 4: Zavodskaya, I.S., *et al.* Biogenic amines (1985), 2(3), 235-41. "Pharmacological analysis of the norepinephrine role in the experimental gastric ulceration".
Document 5: Zavodskaya, I.S., *et al.* Farmakologiya I Toksikologiya (1984), 47(2), 23-8. "Use of neurotropic drugs stimulating tissue trophic processes in the treatment of gastric mucosa ulceration".
Document 6: Zavodskaya, I.S., *et al.* Farmakologiya I Toksikologiya (1983), 46(3), 17-20. "Clinicopharmacological study of some neurotropic drugs in neurogenic diseases of the cardiovascular system and stomach".
Document 7: Chekulaeva, L.I., *et al.* Tkanevaya Biol., Mater. Resp. Soveshch., 2nd (1976), 46-8. "Effect of hydrocortisone and ethymizol on the proliferation of liver and tongue epithelial cells".
Document 8: Anichov, S.V., *et al.* Congr. Hung. Pharmacol. Soc., [Proc.] (1976), Volume Date 1974, 2(6, Symp. Pharmacol. Heart), 59-64.
Document 9: Ketlinskii, S.A., *et al.* Byulleten Eksperimental'noi Biologii I Meditsiny (1977), 83(3), 348-50. "Comparative study of the effect of ethymizol and hydrocortisone on the proliferative activity and protein synthesis in the tongue and liver epithelial cells".
Document 10: Isachenko, V.B., *et al.* Farmakologiya I Toksikologiya (1975), 38(5), 566-8. "Prophylactic and curative action of ethimizol on changes in tissue metabolism of the myocardium during its neurogenic affection".
Document 11: Isachenko, V.B.. Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (1967), 11(1), 32-5. "Relation between the lipolytic enzyme activity and lipidosis of the aortic wall".
Document 12: Ryzhenkov, V.E..Patologicheskaya Fiziologiya I Eksperimental'naya Terapiya (Moscow) (1967), 30(1), 11-14 "Mode of imidazol- and pyrazoldicarboxylic acid derivatives action on the hypophyseal-adrenal system".

Documents 1 to 12:
Each of these documents are directed to various pharmaceutical uses for ethimizol [in the form of an ionic salt]:

- to retard changes in neurotransmitter balance and thus promote tissue repair and wound healing [Document 1].
- to retard changes in antioxidative enzyme activity and levels in neurogenic gastric lesions and thus promote tissue repair and wound healing [Document 2].
- to mitigate the development of duodenal ulcers and thus promote tissue repair and wound healing [Document 3].
- to enhance the reparative processes with respect to neurogenic lesions of the gastric mucosa and thus promote tissue repair and wound healing [Document 4]

CONT:

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,A RU 2200007	10 March 2003	5 March 1999	5 March 1999

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of
CONT

- to enhance the reparative processes with respect to gastric mucosa ulceration and thus promote tissue repair and wound healing [Document 5].
- to treat gastric and myocardial damage of neurogenic origin and thus promote tissue repair and wound healing [Document 6]
- to promote mitotic activity in both tongue and hepatic tissue where the mitotic activity had been and thus promote tissue repair and wound healing [Document 7].
- to accelerate the repair of damaged heart tissue, especially myocardial tissue and thus promote tissue repair and wound healing [Document 8]
- to promote mitotic activity in both tongue and hepatic tissue where the mitotic activity had been suppressed and thus promote tissue repair and wound healing [Document 9]
- to retard decreases in creatine phosphate and noradrenaline which has therapeutic and prophylactic value for damage/injury to myocardial tissue, which in turn promotes tissue repair and wound healing [Document 10].
- to retard changes due to lipidosis in the aortic wall and thus promote tissue repair and wound healing [Document 11]
- to retard inflammations and thus promote tissue repair and wound healing [Document 12]

Conventional wisdom suggests that the ethimizol would indeed ionise in vivo and not be available as a salt. However, it would appear that this would deprotonate, leaving the ethimizol as an anion rather than the cationic species depicted in the present application, which are obtained by reaction with an organic or inorganic acid. Indeed the prior art being based upon ethimizol and any ensuing anionic species would in fact teach away from the generation of the compounds of the present application as cationic entities, as the salts would dissociate in vivo to afford the ionic species, that species being cationic. furthermore, the use of these cationic structural analogues to ethimizol as therapeutic agents would be both novel and inventive. In view of this, all claims are both novel and inventive.

NOTE:

RU 2200007 [reported in the International Search Report] was published after the priority date of the current application. As the priority date for the current application is not in dispute this document does not impact on the novelty or inventiveness of the current claims for the purpose of this report, but may be of relevance in certain jurisdictions.

INDUSTRIAL APPLICABILITY:

Claims 1 to 50 appear to posses an industrial applicability in this jurisdiction. However, in other jurisdictions claims to methods of treatment of human beings [claims 1 to 26] may not be possessed of industrial applicability.

of ethimizole is replaced by a charged imidazolium ring. Such charged compounds are unable to penetrate through the blood-brain barrier, and therefore cannot affect the central nervous system.

The specification of RU1075668 disclosed the synthesis of three compounds within the formula, namely the 1,3-dimethyl,1-methyl-3-ethyl, and 1,3-diethyl compounds, and their ability to prevent development of neurogenic gastric lesions in rats, to promote healing of such lesions, and to increase creatine phosphate levels in the gastric wall, when administered intra-peritoneally. It was suggested that, because of this stimulatory effect on energy metabolism, the compounds might be useful as tissue repair agents.

However, no guidance at all was provided as to how any other condition could be treated, how the compounds should be formulated, or by what routes they should be administered. Only intra-peritoneal administration was disclosed. In particular, there was no general disclosure or suggestion that any of the compounds disclosed in this specification could have any activity in promoting healing of wounds, burns, skin ulcers or the like, in reducing scar formation, in reducing inflammation, in stimulating repair of bone, or in treating myocardial infarction.

We have now found that 1,3-dialkyl-4,5-bis(N-methylcarbamoyl)imidazolium salts promote tissue repair in a variety of settings, and in particular promote wound healing and reduce scar formation. We have also found that that a number of 1,3-dialkyl-4,5-bis(N-methylcarbamoyl)imidazolium salts possess anti-inflammatory and wound healing properties, and that the compounds are active both orally and topically. These compounds demonstrate an anti-inflammatory effect in experimental models of inflammation, have no toxic effects in a variety of assays, and are readily synthesised using simple reaction schemes.

Without wishing to be limited by any proposed

physician or veterinarian, and will depend on the nature and state of the condition to be treated, the age and general state of health of the subject to be treated, the route of administration, and any previous treatment which may have been administered.

The carrier or diluent, and other excipients, will depend on the route of administration, and again the person skilled in the art will readily be able to determine the most suitable formulation for each particular case.

It will be clearly understood that the method of the invention may be used in conjunction with one or more other treatments, such as other therapeutic agents or the use of hyperbaric oxygen or subatmospheric pressure.

In a fourth aspect the invention provides a method of synthesis of a compound of formula I, comprising the step of subjecting an 1-alkyl-4,5-bis(optionally N-substituted carbamoyl)imidazole to alkylation (quaternization) with an alkyl benzenesulfonate to produce the corresponding imidazolium benzenesulfonate, and optionally replacing the benzenesulfonate anion by ion exchange, in which the imidazole moiety is as defined in formula I.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the healing of skin full-thickness wounds at 15 days.

A: control group, self-healing without treatment;

B: experimental group treated with compound (2) (10% cream);

C: control group treated with Spasatel balm;

D: experimental group treated with Solcoseryl

from the group consisting of traumatic wounds, surgical wounds, burns, dehisced surgical incisions, grafts, diabetic ulcers, varicose ulcers, decubitus ulcers (bedsores), trophic ulcers, tropical ulcers, steroid ulcers, indolent ulcers, oral or pharyngeal ulcers, aphthous ulcers, and corneal ulcers; and cervical erosions.

16. A method according to any one of claims 1 to 14, in which the subject is suffering from a condition selected from the group consisting of gastric or duodenal ulcers, and ulcerative colitis.

17. A method according to any one of claims 1 to 14, in which the subject is suffering from a condition selected from the group consisting of myocardial damage, liver damage and bone damage.

18. A method according to claim 17 of stimulating liver regeneration.

19. A method according to claim 15 of reducing or preventing scar formation.

20. A method according to claim 16 of treatment of ulcerative colitis.

21. A method according to claim 15 of treatment of oral or pharyngeal ulceration.

22. A method according to claim 17 of treatment of hepatic cirrhosis or chronic active hepatitis.

23. A method according to claim 16 of treatment of gastric or duodenal ulcers.

24. A method according to claim 17 of treatment of myocardial infarction.

25. A method according to claim 17 of stimulating bone repair.

26. A method according to any one of claims 1 to 25, in which the 1,3-dialkyl-4,5-bis (optionally N-substituted carbamoyl) imidazolium salt is selected from the group consisting of

1,3-dimethyl-4,5-bis(N-methylcarbamoyl)imidazolium benzenesulfonate,

1-methyl-3-ethyl-4,5-bis(N-methylcarbamoyl)imidazolium